

Available online on 15.07.2022 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2011-2022 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited



Open Access Full Text Article



Review Article

Female Obesity: A Probable Cause of Infertility

Nayana B Nair¹, Minnu Skaria^{2*}, R. Sambath Kumar³

¹ Post Graduate Student, Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Namakkal (Dt), Kumarapalayam- 638 183, Tamil Nadu, India

² Assistant Professor, Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Namakkal (Dt), Kumarapalayam- 638 183, Tamil Nadu, India

³ Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Namakkal (Dt), Kumarapalayam- 638 183, Tamil Nadu, India

Article Info:

Abstract



Article History:

Received 18 May 2022
Reviewed 29 June 2022
Accepted 10 July 2022
Published 15 July 2022

Cite this article as:

Nair NB, Skaria M, Sambath Kumar R, Female Obesity: A Probable Cause of Infertility, Journal of Drug Delivery and Therapeutics. 2022; 12(4):216-220

DOI: <http://dx.doi.org/10.22270/jddt.v12i4.5585>

*Address for Correspondence:

Minnu Skaria, Pharm.D, Assistant Professor,
Department of Pharmacy Practice, J.K.K. Nattraja
College of Pharmacy, Namakkal (Dt),
Kumarapalayam-638183, Tamil Nadu, India

Obesity, a serious health problem, is a widespread affliction among women of reproductive age. Obesity and overweight refer to an abnormal and excessive fat deposition that has a negative impact on the body's health. Obesity causes a slew of issues, including social, psychological, demographic, and health issues. It has been associated to elevated health risks like diabetes, hypertension, coronary heart disease, and osteoarthritis, as well as numerous cancers like endometrial, breast, and colon cancers. Hyperandrogenemia is caused by insulin resistance and hyperinsulinemia in obese women. The levels of sex hormone-binding globulin (SHBG) are lower, but leptin levels are higher. Impaired ovulatory function and, as a result, reproductive health could be explained by these changes. Obese women have a reduced probability of giving birth to a healthy infant due to lower implantation and pregnancy rates, greater miscarriage rates, and increased maternal and fetal problems throughout pregnancy. In these people, losing weight has a positive impact on their reproductive outcomes.

Keywords: Obesity, Hyperandrogenemia, Sex hormone-binding globulin (SHBG).

INTRODUCTION

Obesity is a worldwide problem. Obesity continues to rise worldwide, despite efforts to combat it ¹. Overweight persons account for around one billion people in the globe, with over 300 million of these being obese. ²

The most accessible measure of obesity is the body mass index (BMI), or overall body size adjusted for height, because the methods for measuring BMI are widely available. Adiposity (regional or total body fat), adipokine production, and lifestyle factors, on the other hand, may all have a role in the overall obesity-related health risk. ³

The link between obesity and cardiometabolic disease is generally understood by both the medical community and the general public. Obesity also appears to play a significant role in the development of female-specific reproductive health disorders, which have a considerable public health impact. ⁴ Obesity has been linked to a higher risk of breast ⁵ and endometrial cancer. ^{6,7}

Obesity is linked to a number of interconnected diseases, including insulin resistance/diabetes, hypertension, dyslipidemia, and sleep apnea, all of which contribute to the diagnosis of a metabolic syndrome, which shortens life expectancy. ⁸ Obesity-related metabolic alterations may have

an impact on reproduction. Obese women undergoing infertility therapy, on the other hand, may experience additional issues such as the requirement for larger dosages of medicines to induce/stimulate ovulation, oocyte morphological alterations, decreased fertilization and implantation rates, and embryo quality. Obese women undergoing IVF may have lower rates of clinical pregnancy and live births, as well as a higher rate of abortion, as compared to women of normal body weight. ⁹ Obese pregnant women are also more likely to experience maternal and foetal problems like gestational diabetes, hypertensive disorders of pregnancy, and increased neonatal morbidity and death. ¹⁰

The link between obesity and infertility was first discovered in 1934, when Irving Stein and Micheal Leventhal described the 'Stein-Leventhal Syndrome,' which included obesity, hirsutism, and infertility. ¹¹

Infertility is an illness that is commonly described as inability to conceive after twelve or more months of natural fertilization attempts, according to the American Society of Reproductive Medicine Practice Committee, ¹² and it is a growing concern in our society today. According to the World Health Organization, this disease affects up to 50-80 million women worldwide, with a fluctuating incidence that can reach up to 50% of all women in some cases. ¹³

Skin fold thickness, underwater weighing, dual energy x-ray absorptiometry (DEXA), MRI, and infrared spectroscopy can all be used to precisely estimate total body fat,¹⁴ but their use is restricted to research. Simpler measurements of obesity, such as BMI, waist circumference (WC), and waist-hip ratio, are employed in daily clinical practice to assess the degree of obesity (WHR).²

A WHR of more than 0.9 for males and higher than 0.8 for women is generally considered to indicate an elevated risk of cardiovascular disease. It was also discovered that in women with a WHR greater than 0.8, the RRs of irregular menstruation and oligomenorrhea were 1.56 and 2.29, respectively.¹⁵

Table 1: Classification of overweight in adults according to BMI.¹⁶

Classification		
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal	18.5–24.9	Average
Overweight	≥ 25	
Pre-obese	25–29.9	Increased
Obese class I	30–34.9	Moderate
Obese class II	35–39.9	Severe
Obese class III	≥ 40	Very severe

We examine the impact of a changed metabolic state on women's reproductive health, with an emphasis on the consequences of obesity on fertility and the treatment of infertility in obese and overweight women.

LIFESTYLE: DIETARY FACTORS

Inadequate diets, such as those with low calories and protein content or, conversely, those based on a habitual hypercaloric dietary assumption, which result in severe thinness or overweight, have a significant impact on ovarian function and

raise the risk of infertility in women. In this regard, it has been observed that women with a BMI of more than 25 kg/m² take longer to conceive than women with a BMI of less than 19 kg/m², and that obesity and overweight are related with lower pregnancy rates, higher gonadotrophin requirements, and more miscarriage events. Premature labour, gestational diabetes, and hypertension are all linked to having a high BMI during pregnancy.¹⁷

One way through which fat intake can affect reproductive tissues is lipotoxicity.¹⁸⁻²² Excess circulating long-chains saturated fatty acids, which are produced by adipocytes and are received through the food, characterize this process. When adipocytes can no longer retain these fatty acids, fat is stored by non-adipose cell types. This causes an increase in reactive oxygen species generation, which leads to mitochondrial malfunction, endoplasmic reticulum stress, and cell death.²³ Granulosa cells and oocytes are among the reproductive tissues damaged, resulting in delayed oocyte maturation and low oocyte quality.^{22, 24}

ADIPOKINES AND INFERTILITY

Adipokines are signalling molecules produced by adipose cells, and the amount produced depends on the amount of adipose tissue present. Leptin, tumour necrosis factor alpha (TNF), interleukin 6 (IL-6), free fatty acids, and adiponectin are adipokines that may play a role in obesity-related illness.²⁵⁻²⁷ Adipokine imbalances can cause inflammation and a disruption in cell communication, affecting cellular metabolism and function.³

Leptin, for example, may influence reproductive function at the hypothalamic level, delivering both the signal to induce reproductive maturation and the signal to keep the hypothalamic-pituitary-ovarian axis signaling normal.^{25, 28, 29}

The levels of leptin and tumour necrosis factor (TNF) differ between the follicular and luteal phases of the menstrual cycle.²⁵ Although the significance of these differences in adipokines between menstrual cycle phases is unknown, they could influence signalling within the hypothalamic-pituitary-ovarian axis, which is essential for optimal oocyte recruitment and ovulation.³

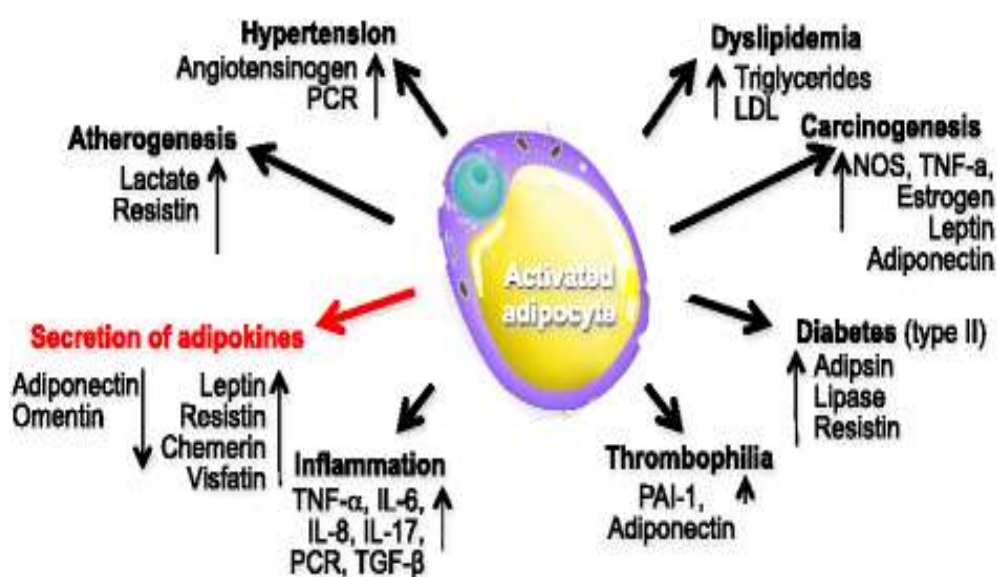


Figure 1 Functional property of adipocytes

Table 2: Major effects of adipokines in fertility of the obese woman. ¹⁷

Adipokines	Serum Levels	Effects
Leptin	↑	Inhibits insulin induced ovarian steroidogenesis Inibiths LH stimulated E2 production by the granulosa cells
Adiponectin	↓	Plasma insulin levels increase
Resistin	↑	Causes insulin resistance
Visfatin	↑	Increased insulin sensitivity
Omentin	↓	Increased insulin sensitivity
Chemerin	↑	Negatively regulates FSH_induced follicular steroidogenesis

LH Luteinizing hormone, FSH Follicle stimulating Hormone, E2 Estradiol

OBESITY, PHYSICAL ACTIVITY AND INFERTILITY

Physical inactivity reduces energy expenditure and contributes to the development and maintenance of obesity. It's uncertain if inactivity and exercise play a role in the pathophysiologic mechanisms that relate obesity to disease.³⁰ Another study using NHSII data that adjusted for BMI found that women with the highest levels of physical activity were less likely to experience ovulatory infertility than those with low levels of physical activity.³¹ Another recent study of physical activity and pregnancy time found that higher levels of physical exercise were linked to a shorter pregnant time.^[32] Obesity is caused and maintained by a combination of poor dietary choices and a lack of physical activity,³⁰ and therefore physical activity may be a key component in improving reproductive function in obese people.³

ENHANCING REPRODUCTIVE FUNCTION IN OBESE WOMEN WITH INFERTILITY

Obese infertile women should first try to lose weight before turning to ovulation-inducing medicines or artificial insemination. Improved menstrual function and fertility, as well as a reduction in metabolic risks, should follow from reducing fat and abdominal fat. Restoration of ovulation, an 11 percent reduction in belly fat, a 4 cm reduction in WC, and a 71 percent increase in insulin sensitivity were all linked to a 2–5% drop in body weight.³³ Weight loss leads to an increase in SHBG (sex-hormone binding globulin), a decrease in testosterone, improved menstrual function, a higher rate of conception, and a lower chance of miscarriage. Abdominal fat removal is crucial in recovering ovulation since central adiposity is linked to menstrual problems and infertility.²

Table 3: NIH clinical guidelines for long-term treatment of overweight and obesity. ³⁴

• Sensible diet and changed eating habits for the long term • Effective physical activity programme sustainable long term • Behaviour modification, reduction of stress, well being • Social support by physician, family, spouse and peers • Smoking cessation and reduction in alcohol consumption • Avoidance of 'crash diets' and short-term weight loss • Minor roles for drugs involved in weight loss • Avoidance of aggressive surgical approaches for majority • Adaptation of weight loss programme to meet individual needs Long-term observation, monitoring and encouragement of patients who have successfully lost weight

DIETARY MANAGEMENT

Calorie restriction, rather than the diet's composition, should be the focus of attention. Obesity diets should strive for gradual weight loss by reduced calorie intake and increased

physical activity, with the overall goal of energy expenditure exceeding energy intake.²

Table 4. Dietary management for weight loss.²

• Energy deficit of 500–600 kcal/day • Low fat (30% of energy), moderate protein (15%) and high carbohydrate (55%) • Increased nonrefined carbohydrate, such as wholegrain bread and cereals • Increased fruits and vegetables • Low-glycemic index food may aid weight loss through increased satiation • No evidence for the strategy of increasing dietary protein to replace carbohydrate
--

BARIATRIC SURGERY AND WEIGHT LOSS

For some women, clinically meaningful weight loss with lifestyle changes may be challenging. Bariatric surgery may result in more significant and long-term weight loss.³

Laparoscopic adjustable gastric banding and laparoscopic Roux-en-Y gastric bypass are the two most popular bariatric procedures performed today. Both of these procedures have outstanding results,^{35,36} with the majority of patients losing more than half of their excess weight and the majority of obesity-related comorbidities, such as diabetes and hypertension, being reversed or avoided.³⁷

After bariatric surgery, menstrual cycle abnormalities may go completely. Menstrual issues and PCOS-related fertility improve significantly after gastric bypass surgery and subsequent weight loss. Infertility caused by anovulation in morbidly obese women could thus be considered an additional rationale for bariatric surgery if other less invasive methods have failed.²

COMPLICATIONS OF BARIATRIC SURGERY

I. Tachycardia

Simple post-operative tachycardia in obese patients is a WARNING SIGNAL and should be treated seriously. Dehydration is the most prevalent cause; however pulmonary embolism or a surgical complication like an anastomotic fistula should also be investigated.³⁸

II. Surgical complications

Peritonitis from anastomotic fistula formation is the most prevalent post-surgery complication. This is a common early complication that occurs within the first 10 days following surgery, with a 1-6 percent^{39,40} incidence after gastric bypass and 3-7 percent after sleeve gastrectomy.⁴¹

III. Pulmonary complications

With a predicted frequency of 2% and a fatality rate of 20-30%, deep vein thrombosis and pulmonary embolism are the second largest cause of post-operative death following gastric surgery.^[15, 16] They may appear a few days after surgery, but the risk remains for several months afterward.

IV. Hepato-biliary complications

Obese people are more likely to have gallstones, which appear to be exacerbated following bariatric surgery (3-30 percent). To try to avoid this problem, urso-deoxycholic acid is frequently administered post-operatively (for 6 months).⁴⁴

V. Gastrointestinal complications

Gastric ulcers can arise in as many as 15% of people who have bypass surgery. The exact reason of this has yet to be determined. These symptoms usually appear during the first 90 days after surgery and include severe dyspepsia, dysphagia, retrosternal discomfort, and/or vomiting.^{45, 46}

PHARMACOLOGICAL TREATMENT

Thyroid hormone, phenylpropanolamine (PPA), a sympathomimetic agent (25mg orally 3 times a day), mazindol, a sympathomimetic amine (3mg/day orally in divided doses), fenfluramines, a serotonergic agonist (0.2mg/kg/day) and more recently, sibutramine, a schedule-IV controlled substance (10mg once daily) and orlistat, a lipase inhibitor (60mg orally 3 times a day) have all been used to treat obesity, with the primary goals of weight loss, weight maintenance, and risk reduction. These substances suppress hunger, reduce fat absorption, and enhance energy

expenditure. However, research on the long-term efficacy of anti-obesity drugs is few.²

CONCLUSION

With the global obesity rate rising, study in this field will undoubtedly continue. Time limits female fertility, the reproductive phenotype of obesity varies, and existing obesity measurements are not accurate predictors of these phenotypes. Finally, while the search for a "magic bullet" to cure obesity will undoubtedly continue, the importance of food, exercise, and lifestyle adjustment must remain at the forefront of obesity management.

ACKNOWLEDGEMENT

We would like to express our thanks to the head, Department of Pharmacy Practice and our Department staffs to their valuable suggestions and recommendations.

CONFLICTS OF INTEREST

Authors declare that they have no conflicts of interest.

FUNDING STATEMENT

This review did not receive any funding.

REFERENCES

1. World Health Organization: Obesity preventing and managing the global epidemic. Report of a WHO consultation on Obesity WHO/NUT/NCD 98.1. World Health Organization, Geneva, Switzerland (1997).
2. Zain MM, Norman RJ. Impact of obesity on female fertility and fertility treatment. *Womens Health (Lond)*. 2008; 4(2):183-194. <https://doi.org/10.2217/17455057.4.2.183>
3. Jungheim ES, Travieso JL, Carson KR, Moley KH. Obesity and reproductive function. *Obstet Gynecol Clin North Am*. 2012; 39(4):479-493. <https://doi.org/10.1016/j.ogc.2012.09.002>
4. American Dietetic Association; American Society of Nutrition, Siega-Riz AM, King JC. Position of the American Dietetic Association and American Society for Nutrition: obesity, reproduction, and pregnancy outcomes. *J Am Diet Assoc*. 2009; 109(5):918-927. <https://doi.org/10.1016/j.jada.2009.03.020>
5. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA*. 2006; 296(2):193-201. <https://doi.org/10.1001/jama.296.2.193>
6. Ballard-Barbash R, Swanson CA. Body weight: estimation of risk for breast and endometrial cancers. *Am J Clin Nutr*. 1996; 63(3 Suppl):437S-41S. <https://doi.org/10.1093/ajcn/63.3.437>
7. Modesitt SC, van Nagell JR Jr. The impact of obesity on the incidence and treatment of gynecologic cancers: a review. *Obstet Gynecol Surv*. 2005; 60(10):683-692. <https://doi.org/10.1097/01.ogx.0000180866.62409.01>
8. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013; 309(1):71-82. <https://doi.org/10.1001/jama.2012.113905>
9. Provost MP, Acharya KS, Acharya CR, et al. Pregnancy outcomes decline with increasing body mass index: analysis of 239,127 fresh autologous in vitro fertilization cycles from the 2008-2010 Society for Assisted Reproductive Technology registry. *Fertil Steril*. 2016; 105(3):663-669. <https://doi.org/10.1016/j.fertnstert.2015.11.008>
10. Aune D, Saugstad OD, Henriksen T, Tonstad S. Maternal body mass index and the risk of fetal death, stillbirth, and infant death: a systematic review and meta-analysis. *JAMA*. 2014; 311(15):1536-1546. <https://doi.org/10.1001/jama.2014.2269>
11. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol*. 29, 181-191. [https://doi.org/10.1016/S0002-9378\(15\)30642-6](https://doi.org/10.1016/S0002-9378(15)30642-6)

12. Habbema JD, Collins J, Leridon H, Evers JL, Lunenfeld B, te Velde ER. Towards less confusing terminology in reproductive medicine: a proposal. *Hum Reprod*. 2004; 19(7):1497-1501. <https://doi.org/10.1093/humrep/deh303>
13. Ombelet W, Cooke I, Dyer S, Serour G, Devroey P. Infertility and the provision of infertility medical services in developing countries. *Hum Reprod Update*. 2008; 14(6):605-621. <https://doi.org/10.1093/humupd/dmn042>
14. Moyad MA. Current methods used for defining, measuring, and treating obesity. *Semin Urol Oncol*. 2001; 19(4):247-256.
15. Hartz AJ, Rupley DC, Rimm AA. The association of girth measurements with disease in 32,856 women. *Am J Epidemiol*. 1984; 119(1):71-80. <https://doi.org/10.1093/oxfordjournals.aje.a113727>
16. Seidell JC. The impact of obesity on health status: some implications for health care costs. *Int J Obes Relat Metab Disord*. 1995; 19(6):S13-S16.
17. Silvestris E, de Pergola G, Rosania R, Loverro G. Obesity as disruptor of the female fertility. *Reprod Biol Endocrinol*. 2018; 16(1):22. <https://doi.org/10.1186/s12958-018-0336-z>
18. Jungheim ES, Schoeller EL, Marquard KL, Loudon ED, Schaffer JE, Moley KH. Diet-induced obesity model: abnormal oocytes and persistent growth abnormalities in the offspring. *Endocrinology*. 2010; 151(8):4039-4046. <https://doi.org/10.1210/en.2010-0098>
19. Jungheim ES, Loudon ED, Chi MM, Frolova AI, Riley JK, Moley KH. Preimplantation exposure of mouse embryos to palmitic acid results in fetal growth restriction followed by catch-up growth in the offspring. *Biol Reprod*. 2011; 85(4):678-683. <https://doi.org/10.1095/biolreprod.111.092148>
20. Wu LL, Dunning KR, Yang X, et al. High-fat diet causes lipotoxicity responses in cumulus-oocyte complexes and decreased fertilization rates. *Endocrinology*. 2010; 151(11):5438-5445. <https://doi.org/10.1210/en.2010-0551>
21. Robker RL, Wu LL, Yang X. Inflammatory pathways linking obesity and ovarian dysfunction. *J Reprod Immunol*. 2011; 88(2):142-148. <https://doi.org/10.1016/j.jri.2011.01.008>
22. Yang X, Wu LL, Chura LR, et al. Exposure to lipid-rich follicular fluid is associated with endoplasmic reticulum stress and impaired oocyte maturation in cumulus-oocyte complexes. *Fertil Steril*. 2012; 97(6):1438-1443. <https://doi.org/10.1016/j.fertnstert.2012.02.034>
23. Schaffer JE. Lipotoxicity: when tissues overeat. *Curr Opin Lipidol*. 2003; 14(3):281-287. <https://doi.org/10.1097/00041433-200306000-00008>
24. Wu LL, Norman RJ, Robker RL. The impact of obesity on oocytes: evidence for lipotoxicity mechanisms. *Reprod Fertil Dev*. 2011; 24(1):29-34. <https://doi.org/10.1071/RD11904>
25. Gosman GG, Katcher HI, Legro RS. Obesity and the role of gut and adipose hormones in female reproduction. *Hum Reprod Update*. 2006; 12(5):585-601. <https://doi.org/10.1093/humupd/dml024>
26. Gosman GG, Katcher HI, Legro RS. Obesity and the role of gut and adipose hormones in female reproduction. *Hum Reprod Update*. 2006; 12(5):585-601. <https://doi.org/10.1093/humupd/dml024>
27. Shuldiner AR, Yang R, Gong DW. Resistin, obesity, and insulin resistance--the emerging role of the adipocyte as an endocrine organ. *N Engl J Med*. 2001; 345(18):1345-1346. <https://doi.org/10.1056/NEJM200111013451814>
28. Tortoriello DV, McMinn J, Chua SC. Dietary-induced obesity and hypothalamic infertility in female DBA/2J mice. *Endocrinology*. 2004; 145(3):1238-1247. <https://doi.org/10.1210/en.2003-1406>
29. Balen AH, Anderson RA; Policy & Practice Committee of the BFS. Impact of obesity on female reproductive health: British Fertility Society, Policy and Practice Guidelines. *Hum Fertil (Camb)*. 2007; 10(4):195-206. <https://doi.org/10.1080/14647270701731290>
30. Wolin KY, Carson K, Colditz GA. Obesity and cancer. *Oncologist*. 2010; 15(6):556-565. <https://doi.org/10.1634/theoncologist.2009-0285>
31. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Diet and lifestyle in the prevention of ovulatory disorder infertility. *Obstet Gynecol*. 2007; 110(5):1050-1058. <https://doi.org/10.1097/01.AOG.0000287293.25465.e1>
32. Wise LA, Rothman KJ, Mikkelsen EM, Sørensen HT, Riis AH, Hatch EE. A prospective cohort study of physical activity and time to pregnancy. *Fertil Steril*. 2012; 97(5):1136-42.e424. <https://doi.org/10.1016/j.fertnstert.2012.02.025>
33. Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *J Clin Endocrinol Metab*. 1999; 84(4):1470-1474. <https://doi.org/10.1210/jc.84.4.1470>
34. Bates GW, Whitworth NS. Effect of body weight reduction on plasma androgens in obese, infertile women. *Fertil Steril*. 1982; 38(4):406-409. [https://doi.org/10.1016/S0015-0282\(16\)46571-4](https://doi.org/10.1016/S0015-0282(16)46571-4)
35. Korenkov M. Bariatric surgery. *Contrib Nephrol*. 2006; 151:243-253. <https://doi.org/10.1159/000095334>
36. Kendrick ML, Dakin GF. Surgical approaches to obesity. *Mayo Clin Proc*. 2006; 81(10):S18-S24. [https://doi.org/10.1016/S0025-6196\(11\)61177-4](https://doi.org/10.1016/S0025-6196(11)61177-4)
37. Escobar-Morreale HF, Botella-Carretero JI. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *J Clin Endocrinol Metab*. 2005; 90(12):6364-6369. <https://doi.org/10.1210/jc.2005-1490>
38. Burgos AM, Braghetto I, Csendes A, et al. Gastric leak after laparoscopic-sleeve gastrectomy for obesity. *Obes Surg*. 2009; 19(12):1672-1677. <https://doi.org/10.1007/s11695-009-9884-9>
39. Westling A, Gustavsson S. Laparoscopic vs open Roux-en-Y gastric bypass: a prospective, randomized trial. *Obes Surg*. 2001; 11(3):284-292. <https://doi.org/10.1381/096089201321336610>
40. Luján JA, Hernandez Q, Frutos MD, Valero G, Cuenca JR, Parrilla P. Laparoscopic gastric bypass in the treatment of morbid obesity. Preliminary results of a new technique. *Surg Endosc*. 2002; 16(12):1658-1662. <https://doi.org/10.1007/s00464-002-9035-z>
41. Kassir R, Debs T, Blanc P, et al. Complications of bariatric surgery: Presentation and emergency management. *Int J Surg*. 2016; 27:77-81. <https://doi.org/10.1016/j.ijsu.2016.01.067>
42. Wittgrove AC, Clark GW. Laparoscopic gastric bypass, Roux-en-Y-500 patients: technique and results, with 3-60 month follow-up. *Obes Surg*. 2000; 10(3):233-239. <https://doi.org/10.1381/096089200321643511>
43. Melinek J, Livingston E, Cortina G, Fishbein MC. Autopsy findings following gastric bypass surgery for morbid obesity. *Arch Pathol Lab Med*. 2002; 126(9):1091-1095. <https://doi.org/10.5858/2002-126-1091-AFFGBS>
44. Sugerman HJ, Brewer WH, Shiffman ML, et al. A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric-bypass-induced rapid weight loss. *Am J Surg*. 1995; 169(1):91-97. [https://doi.org/10.1016/S0002-9610\(99\)80115-9](https://doi.org/10.1016/S0002-9610(99)80115-9)
45. Rasmussen JJ, Fuller W, Ali MR. Marginal ulceration after laparoscopic gastric bypass: an analysis of predisposing factors in 260 patients. *Surg Endosc*. 2007; 21(7):1090-1094. <https://doi.org/10.1007/s00464-007-9285-x>
46. Sacks BC, Mattar SG, Qureshi FG, et al. Incidence of marginal ulcers and the use of absorbable anastomotic sutures in laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2006; 2(1):11-16. <https://doi.org/10.1016/j.soard.2005.10.013>